

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

68

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/215, 9/00, 9/20	A1	(11) International Publication Number: WO 96/37202 (43) International Publication Date: 28 November 1996 (28.11.96)
(21) International Application Number: PCT/US96/06639 (22) International Filing Date: 8 May 1996 (08.05.96) (30) Priority Data: 08/445,849 22 May 1995 (22.05.95) US (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors: GUITTARD, George, V.; 22434 St. Andrews Avenue, Cupertino, CA 95014 (US). JAO, Francisco; 5260 Arrezo Drive, San Jose, CA 95138 (US). MARKS, Susan, M.; 1815 Newport Avenue, San Jose, CA 95125 (US). KIDNEY, David, J.; 1355H Sage Hen Way, Sunnyvale, CA 94087 (US). GUMUCIO, Fernando; 3063 Forbes, Santa Clara, CA 95051 (US). (74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, P.O. Box 10950, 950 Page Mill Road, Palo Alto, CA 94303-0802 (US).	(81) Designated States: AU, CA, CH, DE, ES, GB, JP, KR, MX, NZ. Published <i>With international search report.</i>	
(54) Title: DOSAGE FORM COMPRISING OXYBUTYNIN (57) Abstract A composition comprising oxybutynin and a device comprising oxybutynin are disclosed for oxybutynin therapy.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

DOSAGE FORM COMPRISING OXYBUTYNIN

This invention pertains to a novel dosage form comprising oxybutynin.

The invention relates also to a therapeutic composition comprising
5 oxybutynin, and the invention concerns additionally a method for
administering oxybutynin to a patient in need of oxybutynin.

BACKGROUND OF THE INVENTION

10 Many people are affected by urinary incontinence. Incontinence is
particularly common in the elderly, urinary incontinence is present in
approximately fifty percent of nursing home patients, and urinary incontinence
is a well-known urologic problem in women. It will affect nearly all women in
some form during their lifetime, and it is of significant social concern to all
15 humans who experience it.

Urinary incontinence arises from the anatomy and the physiology of
the urinary tract, which is composed of a bladder and a sphincter.
Anatomically, the bladder consists of the bladder musculature, also known as
20 detrusor, and the trigone. The sphincter includes the bladder neck and the
proximal urethra. The detrusor muscle is innervated by the pelvic nerve
through the parasympathetic nervous system, and the bladder neck and
proximal urethra are innervated by the sympathetic nervous system.

25 The major functions of the bladder are the storage and expulsion of
urine. The bladder is responsible for accommodating increasing volumes of
urine at low pressures. Normally, the bladder remains closed during bladder
filling, and continence is maintained as long as the bladder neck and urethral
pressure exceeds intravesical pressure. Voluntary voiding occurs when
30 intravesical pressure exceeds bladder neck and urethral pressure, and

involuntary voiding occurs when the intravesical pressure exceeds the bladder neck and urethral pressure.

Involuntary incontinence also known as urge incontinence occurs with
5 a loss of large a volume of urine accompanied by symptoms of urgency,
frequency and nocturia caused by an unstable bladder or detrusor instability.
The patient may lose urine with a change in position or with auditory
stimulation. The loss of small volumes of urine usually occurs because of
bladder overdistention by a large amount of residual urine referred to as
10 overflow incontinence.

The management of incontinence consists in administering a smooth-
muscle relaxant such as oxybutynin, which acts directly on the smooth-
muscle at the site distal to the cholinergic receptor. The usual dose in the
15 pharmacologic management is repeated doses from two-to-four times a day
for oxybutynin. This is difficult to achieve as it requires rigid compliance and
it is cost ineffective. Also, oxybutynin is adversely affected by light, and it
needs protection from air which properties do not lend the drug to formulation
into a dosage form that can administer oxybutynin at a controlled and known
20 rate per unit time to produce the intended therapy.

In the light of the above presentation, it will be appreciated by those
versed in the medical and in the pharmaceutical dispensing arts to which this
invention pertains, that a pressing need exists for a dosage form that can
25 deliver the valuable drug oxybutynin in a rate-controlled dose to a patient in
clinical need of incontinence management. The pressing need exists also for
an oral dosage form and for a method of therapy that can deliver oxybutynin
at a controlled rate in a substantially constant dose per unit time for its
beneficial therapeutic effect. The need exists further for a dosage form that
30 can deliver oxybutynin substantially protected from light to insure a complete
dose of oxybutynin is administered to the patient and still remain substantially

independent of the changing environment of the gastrointestinal tract. The need exists additionally for a dosage form that can deliver a therapeutic dose of oxybutynin for its intended effect and also lessen the side-effects that can accompany the drug. It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form and method are made available that can administer oxybutynin in a rate-controlled dose over time, and simultaneously provide oxybutynin for lessening the incident of incontinence, the dosage form and its accompanying method would represent an advancement and a valuable contribution to the medical arts.

10

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering oxybutynin in a rate-controlled dose, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

15

Another object of the present invention is to provide a dosage form for orally administering oxybutynin in a rate-controlled dose for the nonsurgical treatment of incontinence in a human afflicted with incontinence.

20

Another object of the invention is to provide a pharmacologic composition comprising oxybutynin indicated for the pharmacologic management of incontinence.

25

Another object of the present invention is to provide a pharmacologic composition comprising oxybutynin, its racemate, its R-enantiomer and its S-enantiomer administrable to a human for lessening the incidence of incontinence.

30

Another object of this invention is to provide a novel composition that makes available controlled and sustained oxybutynin therapeutic activity to a patient in need of oxybutynin therapy.

5 Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer oxybutynin to a biological receptor to produce the desired oxybutynin effects.

Another object of the present invention is to provide a dosage form
10 manufactured as an osmotic dosage form that maintains oxybutynin and oxybutynin therapeutically acceptable salts in the dosage form and provide protection from light until the oxybutynin is released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment of use and still provide
15 controlled administration of oxybutynin over time.

Another object of the present invention is to provide a dosage form that administers oxybutynin at a controlled rate over time for its therapeutic benefit accompanied by a lessening of possible unwanted side-effects.

20

Another object of the present invention is to provide a dosage form that contains initially crystalline oxybutynin salt protected by a light-resistant semipermeable polymeric wall from light and can be administered in a rate-controlled dose over time.

25

Another object of the present invention is to provide a dosage form adapted for the oral administration of α -cyclohexyl- α -hydroxy-benzeneacetic acid 4-(diethylamino)-2-butynyl ester salt in a first composition in contacting layered arrangement with a second force generating second composition that
30 operates in combination for the controlled administration of the beneficial ester salt.

Another object of the present invention is to provide a complete pharmaceutical oxybutynin regimen comprising a composition comprising oxybutynin that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating incontinence by orally administering oxybutynin from a delivery device in a rate-controlled amount per unit time to a warm-blooded animal in need of incontinence therapy.

Other objects, features and advantages of this invention will be more apparent to those versed in the delivery arts from following detailed specification, taken in conjunction with the accompanying claims.

DETAILED DISCLOSURE OF SPECIFICATION

In one aspect, the present invention provides a therapeutic composition comprising 1 ng to 450 mg (nanogram to milligrams) of oxybutynin, or an oxybutynin therapeutically acceptable salt selected from the group consisting of acetate, bitartrate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, hydrobromide, hydrochloride, lactate, malate, maleate, mandelate, mesylate, methylnitrate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tannate and tartrate. The oxybutynin can be present as the racemate, as the R-enantiomer or as the S-enantiomer. The therapeutic composition further contains 40 mg to 250 mg of a polyalkylene oxide selected from the group consisting of a polyethylene oxide of 200,000 molecular weight or a polyethylene oxide of 300,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 150,000 selected from

the group consisting of hydroxy-propylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose, 1 mg to 40 mg of an osmotic solute selected from the osmotically effective compounds consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric and, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol, and 0.01 mg to 5 mg of a lubricant such as calcium stearate, magnesium stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, and a mixture of salt of fatty, alicyclic or aromatic acid and a fatty, alicyclic or aromatic acid.

The invention provides for the therapeutic composition comprising the oxybutynin to be administered as the composition neat for increasing the urinary bladder capacity, for diminishing the frequency of uninhibited contractions of the detrusor muscles, and its accompanying delay of the desire to void. The invention provides also the therapeutic composition as a therapeutic layer in layered arrangement with a hydrogel layer that supports the therapeutic layer to yield a bi-layered matrix. The hydrogel layer comprises 40 mg to 250 mg of a polyalkylene oxide of 3,000,000 to 8,000,000 molecular weight selected from the group consisting of polyethylene oxide and polypropylene oxide, or 40 mg to 250 mg of an alkali carboxymethylcellulose of 10,000 to 6,000,000 molecular weight such as sodium carboxymethylcellulose or potassium carboxymethylcellulose, 1 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol, 0 mg to 5 mg of ferric oxide, 0.1 mg to 30 mg of a hydroxyalkylcellulose of 7,500 to 175,000 molecular weight, or 0.1 mg to 30 mg of a hydroxypropylalkyl cellulose of 9,000 to 225,000 molecular weight selected from the group consisting of hydroxy ethylcellulose,

hydroxypropylmethylcellulose, hydroxypropylcellulose, and hydroxypropylethylcellulose, 0.00 to 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylatedhydroxyquinone, butylhydroxyanisol, hydroxycomarin, butylated
5 hydroxytoluene, cephalin, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propylhydroxybenzoate, trihydroxybutylphenone, dimethylphenol, di-tert-butylphenol, vitamin E, lecithin and ethanolamine, and 0.2 mg to 7 mg of a lubricant selected from the group consisting of calcium stearate, magnesium stearate, magnesium oleate, calcium palmitate, sodium suberate,
10 potassium laureate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic or aromatic acid.

The invention further provides a delivery device for the delivery of the
15 therapeutic composition comprising oxybutynin. The delivery device comprises a wall, which wall surrounds an internal compartment. The wall is semipermeable, as it is permeable to the passage of fluid and impermeable to the passage of oxybutynin. The wall is nontoxic and it comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate,
20 cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 weight percent, (wt%) to 100 wt% of the cellulosic wall-forming polymer, or the wall can comprise 0.01 wt% to 10 wt% of polyethylene glycol, or 1 wt% to 25 wt% of a cellulose either selected from the group consisting of hydroxypropylcellulose and
25 hydroxypropylmethylcellulose. The total weight percent of all components comprising wall 12 is equal to 100 wt%. The internal compartment comprises the therapeutic oxybutynin composition in layered position with the expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension and thereby occupies space in the
30 compartment. The therapeutic layer and the expandable layer act together during the operation of the delivery device for the controlled release of

oxybutynin to a patient over time. The delivery device comprises a passageway in the wall that connects the exterior of the delivery device with the internal compartment. The delivery device provided by the invention delivers oxybutynin from the device to the patient at a substantially zero order
5 rate of release over a period of twenty-four hours.

The expression passageway, comprises means and methods suitable for the metered release of the therapeutic drug 18 from compartment 15 of dosage form 10. The exit means 13 comprises at least one passageway,
10 orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, porous overlay, and porous element that provides for the osmotic controlled release of oxybutynin. The expression passageway includes a material that erodes or is leached from the wall in a fluid environment of use to produce at least one dimensioned passageway. Representative materials suitable for
15 forming a passageway, or a multiplicity of passageways comprise a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous filament, poly(vinyl alcohol), leachable polysaccharides, salts and oxides. A pore passageway, or more than one pore passageways can be formed by leaching a leachable compound, such as sorbitol, from the wall. The
20 passageway possessing controlled release dimensions such as round, triangular, square, elliptical, and the like, for the metered release of oxybutynin from the delivery device. The delivery device can be constructed with one or more passageways in spaced apart relationship on a single surface or on more than one surface of the wall. Passageways and
25 equipments for forming passageways are disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864 and 4,816,263. Passageways formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 and 4,285,987.

**DESCRIPTION OF PROCESSES FOR MANUFACTURING
THE DOSAGE FORM OF THE INVENTION**

The wall of the delivery device can be formed in one technique using
5 the air suspension procedure. This procedure consists in suspending and
tumbling the compressed layers in a current of air and wall-forming
composition until a wall is applied to the oxybutynin forming compartment.
The air suspensions procedure is well-suited for independently forming the
wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241;
10 *J. Am. Pharm. Assoc.*, Vol. 48, pages 451 to 459, 1959; and *ibid.* Vol. 49,
pages 82 to 84, 1960. The wall can also be formed with a wall-forming
composition in a Wurster® air suspension coater, using acetone-water co-
solvent, 90:10, wt:wt, using 2.5 to 7 wt% polymer solids. The
Aeromatic® air suspension coater using a methylene dichloride methanol co-
15 solvent, 87:13, v:v, also can be used for applying the wall. Other wall forming
techniques, such as pan coating, can be used for providing the delivery
device. In the pan coating system, wall forming compositions are deposited
by successive spraying of the composition on the bi-layered compartment,
accompanying by tumbling in a rotating pan. A larger volume of co-solvent
20 can be used to reduce the concentration of polymer solids to produce a
thinner wall. Finally, the wall coated compartments are laser or mechanically
drilled, and then dried in a forced air or humidity oven for 3 days to a week to
free the solvent. Generally, the walls formed by these techniques have a
thickness of 2 to 20 mils (0.051 to 0.51 mm) with a presently preferred
25 thickness of 2 to 6 mils (0.051 to 0.15 mm).

The delivery device of the invention is manufactured by standard
manufacturing techniques. For example, in one manufacture, the beneficial
oxybutynin and other ingredients comprising the first layer facing the exit
30 m ans are blended and pressed into a solid layer. The oxybutynin and other
ingr dients can be bl nd d also with a solv nt and into a solid or s misolid

formed by conventional methods such as ball-milling, calendering, stirring or rollmilling and then pressed into a preselected shape. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the delivery device and it also possesses dimensions

5 corresponding to the second layer for forming a contacting arrangement therewith. Next, the oxybutynin hydrogel layer is placed in contact with the oxybutynin layer. The layering of the oxybutynin layer and the hydrogel layer can be fabricated by conventional press-layering techniques. Finally, the two layer compartment forming members are surrounded and coated with an

10 outer wall. A passageway is laser drilled through the wall to contact the oxybutynin layer, with the delivery device optically oriented automatically by the laser equipment for forming the passageway on the preselected surface.

In another manufacture, the delivery device is manufactured by the wet

15 granulation technique. In the wet granulation technique, the oxybutynin and the ingredients comprising the first layer are blended using an organic or inorganic solvent, such as isopropyl alcohol-methylene dichloride 80/20 v/v as the granulation fluid. Other granulating fluid, such as water or denatured alcohol 100%, can be used for this purpose. The ingredients forming the first

20 layer are individually passed through a 40 mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the first layer are dissolved in a portion of the granulation fluid, such as the co-solvent described above. Then, the latter prepared wet blend is slowly added to the oxybutynin blend with continual mixing in the blender. The granulating fluid is

25 added until a wet blend is produced, which wet mass then is forced through a 20 mesh screen onto oven trays. The blend is dried for 18 to 24 hours at 25°C to 40°C. The dry granules are screened then with a 16 mesh screen. Next, a lubricant is passed through an 60 mesh screen and added to the dry screened granule blend. The granulation is put into milling jars and mixed on

30 a jar mill for 2 to 10 minutes. The first and second layer compositions are pressed into a layered tablet, for example, in a Manesty® layer press.

Another manufacturing process that can be used for providing the oxybutynin and hydrogel composition comprises blending their powdered ingredients in a fluid bed granulator. After the powdered ingredients are dry
5 blended in the granulator, a granulating fluid, for example poly(vinyl-pyrrolidone) in water, is sprayed onto the respective powders. The coated powders are then dried in a granulator. This process coats-agglomerates all the ingredients present therein while spraying the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is
10 blended as above into the mixture. The granules are pressed then in the manner described above. In an embodiment, when the fluid bed granulating process is used to manufacture the hydrogel layer, the antioxidant is initially present in the polyalkylene oxide by the manufacturer, it is removed during processing. Thus, if an antioxidant is desired, it becomes necessary to add
15 additional antioxidant to the hydrogel formulation, and this addition can be accomplished during the fluid bed granulation described above.

The device of this invention is manufactured in another embodiment by mixing the oxybutynin with composition forming ingredients and pressing the
20 composition into a solid layer possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to a passageway. In another embodiment, the oxybutynin and other first composition forming ingredients and a solvent are mixed into a solid, or semi-solid, by conventional methods such as ballmilling, calendering, stirring or rollmilling,
25 and then pressed into a preselected layer forming shape.

In the manufactures as presented above, the manufacture comprising a layer of a composition comprising an osmopolymer hydrogel and an optional osmagent are placed in contact with the layer comprising the drug
30 oxybutynin and the two layers comprising the layers are surrounded with a semipermeable wall. The layering of the first drug oxybutynin composition

and the second osmopolymer hydrogel and optional osmagent composition can be accomplished by using a conventional two-layer tablet press technique. The wall can be applied by molding, spraying or dipping the pressed shapes into wall forming materials. Another and presently preferred
5 technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layers in a current of air until the wall forming composition surrounds the layers. Manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol. 46, pp 62-70 (1969); and in *Pharmaceutical Science*, by
10 Remington, 14th Ed., pp 1626-1979, (1970), published by Mack Publishing Co., Easton, PA. The delivery device can be manufactured by following the teaching in U.S. Pat. Nos. 4,327,725, 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

15 Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents that do not adversely harm the materials and the final wall of the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons,
20 halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptaene, ethylene glycol monoethyl ether,
25 ethylene glycol monoethylacetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cycl-octane, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and
30 methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DISCLOSURE OF EXAMPLES
PROVIDED BY THE INVENTION

5 The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

10

EXAMPLE 1

 The therapeutic oxybutynin composition provided by the invention was prepared as follows: first, 103 grams of oxybutynin hydrochloride was
15 dissolved in 1200 millimeters of anhydrous ethanol. Separately, 2,280 g of polyethylene oxide of 200,000 molecular weight, 150 g of hydroxypropylmethylcellulose of 9,200 molecular weight and 450 g of sodium chloride were dry blended in a conventional blender for 10 minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution was added slowly,
20 with the mixer continuously blending until all the solution was added to the three component dry blend, with the mixing continued for another 8 to 10 minutes. The blended wet composition was passed through a 16 mesh screen and dried over night at a room temperature of 72°F. (22.2°). Then, the dry granules were passed through a 20 mesh screen and 18 g of
25 magnesium stearate were added and all the ingredients blended again for 5 minutes. The fresh granules are ready for formulation into a therapeutic oxybutynin composition. The therapeutic composition comprises 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 molecular weight, 5 wt% of hydroxypropylmethylcellulose of 9,200 molecular weight,
30 15 wt % sodium chloride, and 0.6 wt % mageseum stearate. The therapeutic composition can b administered as th composition for its intended therapy.

EXAMPLE 2

The osmopolymer, hydrogel composition provided by the invention
5 was prepared as follows: first 1274 g of pharmaceutically acceptable
polyethylene oxide comprising a 7,500,000 molecular weight, 600 g of sodium
chloride, and 20 g ferric oxide were separately screened through a 40 mesh
screen. Then, all the screened ingredients were mixed with 100 g of
hydroxypropylmethylcellulose of 11,200 molecular weight to produce a
10 homogenous blend. Next, 300 ml of denatured anhydrous alcohol was added
slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of
butylated hydroxytoluene was added followed by more blending with 5 g of
magnesium stearate added with 5 minutes of blending to yield a homogenous
blend. The freshly prepared granulation is passed through a 20 mesh screen
15 and allowed to dry for 20 hours at 22.2°C. The final composition comprised
63.67 wt% of the polyethylene oxide, 30 wt % of sodium chloride, 1 wt % of
ferric oxide, 5 mg of hydroxypropylmethylcellulose, 0.08 wt % of butylated
hydroxytoluene, and 0.25 mg of magnesium stearate.

EXAMPLE 3

20 The osmopolymer, hydrogel composition provided by the invention
was prepared as follows: first 1274 g of pharmaceutically acceptable sodium
carboxymethylcellulose comprising a 5,250,000 molecular weight, 600 g of
25 sodium chloride, and 20 g ferric oxide were separately screened through a 40
mesh screen. Then, all the screened ingredients were mixed with 100 g of
hydroxypropylmethylcellulose of 11,200 molecular weight, and 100 g of
hydroxypropylcellulose of 30,000 molecular weight to produce a homogenous
blend. Next, 300 ml of denatured anhydrous alcohol was added slowly to the
30 blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated
hydroxytoluene was added followed by more blending with 5 g of magnesium

stearate added with 5 minutes of blending to yield a homogenous blend. The freshly prepared granulation is passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 58.67 wt% of the sodium carboxymethylcellulose, 30 wt% of sodium chloride, 1 wt% of ferric oxide, 5 mg of hydroxypropylmethylcellulose, 5 mg of hydroxypropylcellulose, 0.08 wt% of butylated hydroxytoluene, and 0.25 mg of magnesium stearate.

EXAMPLE 4

10

The therapeutic oxybutynin composition and the osmopolymer hydrogel composition were made into a bilayer tablet as follows: first, 147 mg of the oxybutynin composition was added to a punch die set, and tamped, then, 98 mg of the hydrogel composition was added and the two layers compressed under a pressure head of 1.0 ton (1000 kg) into a 11/32 inch (0.873 cm) diameter, contacting intimate bilayered tablet.

EXAMPLE 5

20

The bilayered tablet was manufactured into a delivery device as follows: first, a semipermeable wall-forming composition was prepared comprising 95 wt% cellulose acetate having a 39.8% acetyl content and 5 wt % polyethylene glycol having a molecular weight of 3350 by dissolving the ingredients in a co-solvent comprising acetone and water in 90:10 wt:wt composition to make a 4% solid solution. The wall-forming composition was sprayed onto and around the bilayered core to provide a 26.4 mg semipermeable wall.

Next, the semipermeable walled bilayered tablet was laser drilled through the semipermeable wall to provide a 20 mil (0.51 mm) to contact the oxybutynin layer with the exterior of the delivery device. The residual solvent

30

was removed by drying for 48 hours at 50°C and 50% relative humidity. Next the delivery devices were dried further for 1 hour at 50°C to remove excess moisture. The delivery device provided by this manufacture provides 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 molecular weight, 0.6 wt% magnesium stearate, and 15 wt % sodium chloride in the therapeutic oxybutynin composition. The osmopolymer, hydrogel push composition comprises 63.67 wt % polyethylene oxide of 7,500,000 molecular weight, 30 wt % sodium chloride, 1 wt % ferric chloride, 5 wt % hydroxypropylmethylecellulose of 9,200 molecular weight, 0.08 wt % butylated hydroxytoluene, and 0.25 wt % magnesium stearate. The semipermeable wall comprises 95 wt % cellulose acetate comprising 39.8% acetyl content, and 5 wt % polyethylene glycol of 3350 molecular weight. The delivery device comprises an exit passage of 20 mils (0.50mm) and it has a mean release rate of 0.260 mg/hr for 23.8 hours. The semipermeable wall provides substantial protection from photo (light) degradation of the oxybutynin in the delivery device.

EXAMPLE 6

20

A dosage form, prepared according to the above, comprising a drug layer consisting of 6.67 wt% oxybutynin hydrochloride, 87.83 wt% polyethylene oxide of 200,000 molecular weight, 5.00 wt% hydroxypropylmethylcellulose, and 0.50 wt% magnesium stearate; in layered contact with a push layer comprising 58.75 wt% sodium carboxymethylcellulose, 30 wt% sodium chloride 5.00 wt% hydroxypropylmethylcellulose, 1.00 wt% ferric oxide, 5.00 wt% hydroxypropylcellulose and 0.25 wt% magnesium stearate; which bilayered core is surrounded by a semipermeable wall comprising cellulose acetate and polyethylene glycol; and an exit port through the wall for delivering the oxybutynin at a controlled rate over thirty hours.

30

EXAMPLE 7

The dosage form according to claim 6 wherein hydroxypropylmethylcellulose is a member selected from the group consisting of 9,200 and 11,200 molecular weight; the polyethylene oxide has a 300,000 molecular weight; the sodium carboxymethylcellulose is a member selected from the group consisting of 700,000 or 800,000 or 900,000 or 1,000,000 molecular weight; the hydroxypropylcellulose is a member selected from the group consisting of 25,000 or 30,000 or 40,000 molecular weight; and the dosage form comprises 5 mg to 250 mg of oxybutynin pharmaceutically acceptable salt.

**DISCLOSURE OF USE OF THE DOSAGE FORM FOR
PERFORMING A METHOD OF PRACTICING THE INVENTION**

The invention pertains additionally to the use of the delivery device by providing a method for delivering oxybutynin at a controlled rate orally to a warm-blooded animal in need of oxybutynin therapy, wherein the use comprises the steps of: (A) admitting into the warm-blooded animal a delivery device expressing a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of oxybutynin; (2) an oxybutynin layer in the compartment comprising oxybutynin; (3) a hydrogel push layer in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for expanding in size for pushing the oxybutynin composition from the delivery device; (4) at least one passageway in the wall for releasing the oxybutynin; (B) imbibing fluid through the semipermeable wall at a fluid-imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand; and (C) delivering the therapeutically active oxybutynin from the delivery

device through the exit passageway to a warm-blooded animal over a prolonged period of time up to 24 hours. The oxybutynin is administered by the method of the invention for antispasmodic therapy. The oxybutynin is administered to patients with uninhibited neurogenic and reflex neurogenic
5 bladder for increased vesical capacity which diminishes the frequency of uninhibited contractions of the detrusor muscle and delays the desire to void. The dosage form is indicated for the relief of symptoms associated with voiding such as urgency, urge incontinence, frequency, nocturia and incontinence in patients in neurogenic bladder.

10

The dosage form of this invention, as seen from the above disclosure can be used in a method for administering a drug by the oral route, and in another method, the dosage form can be sized and shaped for administering a drug by the sublingual and buccal routes. The sublingual and buccal
15 routes can be used for quicker therapy and they can be used when a smaller dose of drug is needed for immediate therapy. The latter routes can be used as a by-pass of the first pass of hepatic metabolism of the drug.

In summary, it will be appreciated that the present invention
20 contributes to the art an unobvious dosage form that possesses practical utility, can administer a drug at a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof, it will be understood by those skilled in the art that various changes, modifications, substitutions and
25 omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embraces those equivalents within the scope of the claims which follow.

We claim:

1. A therapeutic composition comprising: 1 ng to 450 mg of oxybutynin, 40 mg to 250 mg of a polyalkylene oxide of 200,000 to 300,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 150,000 molecular weight, and 0.01 mg to 5 mg of a lubricant.
2. The therapeutic composition according to claim 1, wherein the oxybutynin is a therapeutically acceptable salt selected from the group consisting of acetate, bitartrate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, hydrobromide, hydrochloride, lactate, malate, maleate, mandelate, mesylate, methylnitrate, mucate, napsylate, nitrate pamoate, pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tannate and tartrate.
3. A bilayered tablet comprising a therapeutic layer comprising 1 ng to 450 mg of oxybutynin, 40 mg to 450 mg of a polyalkylene oxide of 200,000 to 300,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 150,000 molecular weight and 0.01 mg to 5 mg of a lubricant, in contact with a hydrogel layer comprising 40 mg to 250 mg a polyalkylene oxide having a 3,000,000 to 8,000,000 molecular weight, 10 mg to 50 mg of an osmagent, 0.1 mg to 20 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 molecular weight, 0.0 ng to 1.5 mg of an antioxidant and 0.2 mg to 7 mg of a lubricant.
4. A bilayered tablet comprising a therapeutic layer comprising a therapeutic layer comprising 1 ng to 450 mg of oxybutynin, 40 mg to 250 mg of polyalkylene oxide of 200,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 150,000 molecular weight, and 0.01 mg to 5 mg of a lubricant, said layer in contact with a push layer comprising 40 mg to 250 mg of an alkali carboxymethylcellulose of 10,000 to

6,000,000 molecular weight, 10 mg to 50 mg of an osmagent, 0.1 mg to 20 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 molecular weight, 0.1 mg to 30 mg of a hydroxyalkylcellulose of 7,500 to 175,000 molecular weight, 0.0 ng to 1.5 mg of an antioxidant, and 0.2 mg to 7 mg of a lubricant.

5

5. A delivery device for administering oxybutynin to a patient in need of oxybutynin, wherein the delivery device comprises: a layer comprising 1 ng to 450 mg of oxybutynin, 40 mg to 250 mg of a polyalkylene oxide of 200,000 to 300,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 250,000 molecular weight, and 1 mg to 50 mg of an osmagent, and contacting layer comprising 40 mg to 250 mg of an osmopolymer and 10 mg to 50 mg of an osmagent; a semipermeable wall that surrounds the layers, which semipermeable wall is permeable to the passage of fluid, and impermeable to the passage of oxybutynin, and an exit through the semipermeable wall for administering the oxybutynin to the patient at a controlled rate over time.

6. A delivery device for administering oxybutynin to a patient in need of oxybutynin, wherein the delivery device comprises: a drug layer comprising 1 ng to 450 mg of oxybutynin, 40 mg to 250 mg of a polyalkylene oxide of 200,000 to 300,000 molecular weight, 1 mg to 25 mg of a hydroxypropylalkylcellulose of 9,000 to 250,000 molecular weight, 1 mg to 50 mg of an osmagent, and a contacting displacement layer comprising 40 mg to 250 mg of carboxymethylcellulose 10,000 to 6,000,000 molecular weight and 10 mg to 50 mg of an osmagent; a semipermeable wall that surrounds the layers, which semipermeable wall is permeable to the passage of fluid, and impermeable to the passage of oxybutynin, and an exit through the semipermeable wall for administering the oxybutynin to the patient at a controlled rate over time.

30

7. A delivery device for administering oxybutynin to a patient in need of oxybutynin, wherein the delivery device comprises: a drug layer comprising 1 ng to 450 mg of oxybutynin, 40 mg to 250 mg of a polyalkylene oxide of 200,000 to 300,000 molecular weight, 1 mg to 25 mg of a
- 5 hydroxypropylalkylcellulose of 9,000 to 250,000 molecular weight, 1 mg to 50 mg of an osmagent, and a contracting displacement layer comprising 40 mg to 250 mg of a polyalkylene oxide having a 3,000,000 to 8,000,000 molecular weight, and 10 mg to 50 mg of an osmagent; a semipermeable wall that surrounds the layer, which semipermeable wall is permeable to the
- 10 passage of fluid, and impermeable to the passage of oxybutynin, and an exit through the semipermeable wall for administering the oxybutynin to the patient at a controlled rate over time.

INTERNATIONAL SEARCH REPORT

In. ional Application No

PCT/US 96/06639

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/215 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 399 359 (A. R. BAICHWAL) 21 March 1995 see the whole document ---	1-7
A	CHEMICAL ABSTRACTS, vol. 120, no. 18, 2 May 1994 Columbus, Ohio, US; abstract no. 227011, XP002010328 see abstract & JP,A,06 009 388 (KODAMA KK,JP) 18 January 1994 --- -/--	1-7

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

7 August 1996

Date of mailing of the international search report

13.08.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 96/06639

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 120, no. 14, 4 April 1994 Columbus, Ohio, US; abstract no. 173499, XP002010329 see abstract & JP,A,05 339 151 (KODAMA KK,JP) 21 December 1993</p> <p>-----</p>	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/06639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5399359	21-03-95	AU-B- 6588894	18-09-95
		CA-A- 2161103	08-09-95
		CN-A- 1111507	15-11-95
		EP-A- 0700284	13-03-96
		FI-A- 955215	01-11-95
		HU-A- 72981	28-06-96
		WO-A- 9523593	08-09-95

McLoud, B tty (Woodcock Washburn)

Fr m: Trevisani, Ann (Woodcock Washburn)
Sent: Tuesday, December 30, 2003 11:50 AM
T : Davies, Jaclyn (Woodcock Washburn); McLoud, Betty (Woodcock Washburn); File46 (Woodcock Washburn)
Cc: Wilkinson, Deb (Woodcock Washburn)
Subject: RE: Please forward the following U.S. files to me as soon as possible.

Sorry, I don't have any of those files. Ann

-----Original Message-----

From: Davies, Jaclyn (Woodcock Washburn)
Sent: Tuesday, December 30, 2003 11:25 AM
To: McLoud, Betty (Woodcock Washburn); File46 (Woodcock Washburn)
Cc: Trevisani, Ann (Woodcock Washburn); Wilkinson, Deb (Woodcock Washburn)
Subject: RE: Please forward the following U.S. files to me as soon as possible.

Haven't had time to check, sorry... but it's possible. File room, can you search DAC and my areas? Thanks.

Jaclyn R. Davies
Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Phone: 215-568-3100
Fax: 215-568-3439
www.woodcock.com

This e-mail message and any attachments are confidential and may be attorney-client privileged and/or attorney work product. If you are not the intended recipient please notify Woodcock Washburn LLP immediately by telephone at (215) 568-3100 or by e-mail addressed to "postmaster@woodcock.com" and destroy all copies of this message and any attachments.

-----Original Message-----

From: McLoud, Betty (Woodcock Washburn)
Sent: Tuesday, December 30, 2003 6:31 AM
To: File46 (Woodcock Washburn)
Cc: Trevisani, Ann (Woodcock Washburn); Davies, Jaclyn (Woodcock Washburn); Wilkinson, Deb (Woodcock Washburn)
Subject: Please forward the following U.S. files to me as soon as possible.

CEPH-1235
CEPH-2289
CEPH-2311
CEPH-2361

UNGR-1630

Thank you for your assistance.